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A randomized controlled trial

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DOI

[10.1016/j.josat.2025.209878](https://doi.org/10.1016/j.josat.2025.209878)

Publication date

2026

Document Version

Final published version

Published in

Journal of Substance Use and Addiction Treatment

License

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[Link to publication](#)

Citation for published version (APA):

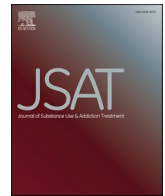
Lortye, S., Faber, N. N. M., Will, J. P., Marquenie, L. A., Lommerse, N. M., Goudriaan, A. E., Arntz, A., & de Waal, M. M. (2026). Timing and type of posttraumatic stress disorder treatment in patients with co-occurring substance use disorder and posttraumatic stress disorder: A randomized controlled trial. *Journal of Substance Use and Addiction Treatment*, 183, Article 209878. <https://doi.org/10.1016/j.josat.2025.209878>

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Timing and type of posttraumatic stress disorder treatment in patients with co-occurring substance use disorder and posttraumatic stress disorder – A randomized controlled trial

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ARTICLE INFO

Keywords:

Posttraumatic stress disorder (PTSD)
Substance use disorder (SUD)
Prolonged exposure (PE)
Eye movement desensitization and reprocessing (EMDR)
Imagery rescripting (ImRs)

ABSTRACT

Introduction: Co-occurrence of posttraumatic stress disorder (PTSD) and substance use disorder (SUD) is common and difficult to treat. Understanding which timing and type of PTSD treatment is most effective for treating PTSD in patients with SUD and PTSD is important to improve treatment outcomes. This study compared effectiveness of simultaneous versus sequential SUD-PTSD-treatment and compared Prolonged Exposure (PE), Eye Movement Desensitization and Reprocessing (EMDR), and Imagery Rescripting (ImRs) head-to-head in patients with co-occurring SUD and PTSD.

Method: A single-blind 6-arm randomized controlled trial with 209 patients with co-occurring SUD and PTSD at two addiction treatment centers in the Netherlands, providing intra- and extramural care. Patients were allocated to simultaneous SUD + PE, SUD + EMDR or SUD + ImRs treatment or sequential SUD-PTSD-treatment (25% each). Next, sequential SUD + PTSD patients were randomly assigned to PE, EMDR, or ImRs (33% each). Data were collected at baseline, 3-month, 6-month, and 9-month follow-up. All analyses were intention-to-treat.

Participants were randomized to receive 12 PTSD treatment sessions of simultaneous SUD + PE ($n = 53$), simultaneous SUD + EMDR ($n = 50$), simultaneous SUD + ImRs ($n = 55$), sequential SUD + PE ($n = 17$), sequential SUD + EMDR ($n = 17$) or sequential SUD + ImRs ($n = 17$). Standard protocols were used.

Primary outcome was clinician-administered PTSD symptom severity. Secondary outcomes were treatment completion and SUD-severity. Additionally, loss of PTSD diagnosis and full remission of PTSD criteria were tested. Linear-Mixed-Models with a two-level structure (repeated measures, patients), were used to investigate treatment-effects.

Results: In the primary analyses including the 6-month and 9-month follow up, no significant differences in PTSD-severity were found between timing nor treatment-types. However, simultaneous treatment outperformed sequential treatment at 3-month follow-up and was preferred by most participants. ImRs was superior to PE and EMDR regarding PTSD-treatment completion. No between-group differences in SUD outcomes were found.

Conclusions: EMDR and ImRs are effective alternatives to the more established PE. These findings indicate that delaying PTSD treatment until after SUD treatment is not necessary.

1. Introduction

The co-occurrence of post-traumatic stress disorder (PTSD) and substance use disorder (SUD) is high (Driessen et al., 2008), and treating

both disorders together is complicated (Najavits, 2002). In general, effect sizes are low and drop-out rates are high (Roberts et al., 2016; Roberts et al., 2022). One previous RCT attempted to reduce drop-out rates by adding motivational sessions but reported no significant

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<https://doi.org/10.1016/j.josat.2025.209878>

Received 20 June 2025; Received in revised form 4 December 2025; Accepted 31 December 2025

Available online 9 January 2026

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difference compared to treatment without these motivational sessions (Coffey et al., 2016). There remains a lack of agreement with regard to the optimal timing of PTSD treatment within the course of SUD treatment, and the optimal type of PTSD treatment for these patients also remains unclear.

At the time of conducting this study, international guidelines (e.g. APA; ISTSS; NICE) did not provide explicit recommendations regarding the timing of trauma-focused treatment relative to SUD treatment. More recent guidelines, including the 2025 APA guidelines, advocate for offering trauma-focused treatments concurrently with SUD treatment, thereby implying a preference for simultaneous rather than sequential approaches (American Psychiatric Association [APA], 2025). Furthermore, a recent expert recommendation advised not waiting for abstinence before initiating PTSD treatment, but also stated that further studies are needed to investigate the differential effects of sequential and simultaneous or integrated treatment (Roberts et al., 2023). However, to date, direct empirical comparisons between simultaneous (or integrated) and sequential treatment remain scarce. Notably, only one study in veterans compared sequential treatment with integrated treatment and found no significant differences in PTSD severity, SUD severity or treatment dropout (Kehle-Forbes et al., 2019). The Dutch guidelines also recommend simultaneous treatment (Snoek et al., 2012), although the supporting evidence base for this recommendation is still limited. With regard to treatment type, information about the most effective type of PTSD treatment is lacking. Only Prolonged Exposure (PE) has been extensively researched for individuals with both PTSD and SUD, demonstrating effectiveness. However, its impact is less pronounced compared to those with PTSD alone, and dropout rates remain high (Roberts et al., 2016). Eye Movement Desensitization and Reprocessing (EMDR) is a well-established PTSD therapy (Lewis, Roberts, Andrew, et al., 2020; Roberts et al., 2023), but research on its use in those with co-occurring SUD is limited to a few pilot studies (Bashir et al., 2023; Perez-Dandieu & Tapia, 2014). At the start of this study, Imagery Rescripting (ImRs) was not yet included in treatment guidelines for PTSD, but was considered a promising approach due to its potential to reduce dropout rates (Boterhoven de Haan et al., 2020). Since then, ImRs has been included in the most recent Dutch multidisciplinary PTSD treatment guidelines (Vereniging & Specialisten, 2025), however, its use has not been explored in patients with co-occurring SUD. Moreover, head-to-head comparisons of all three treatment types are lacking in general, also in PTSD patients without SUD. A previous article from the same research group concluded that PTSD treatment as add-on to SUD treatment is more effective in reducing PTSD symptoms compared to SUD treatment only, however results for PE were somewhat ambiguous depending on the type of analysis used (PE was found only significant without imputed data) (Lortye et al., 2025).

Better insight into optimal treatment timing and treatment type for patients with SUD and PTSD could help to improve treatment adherence and contribute to the development of clearer, more standardized guidelines.

The current study builds on previous work evaluating the effectiveness of PE, EMDR and ImRs as add-on to manualized SUD treatment in patients with SUD and PTSD (Lortye et al., 2025). In the current report, the study aims to 1) compare effectiveness of simultaneous SUD and PTSD treatment with sequential SUD and PTSD treatment; and 2) explore differential effectiveness between three trauma-focused PTSD treatments (PE vs EMDR; PE vs ImRs; EMDR vs ImRs). The primary outcome for both aims was PTSD severity. Secondary outcomes were SUD severity and treatment completion. With regard to aim 1, it was hypothesized that the simultaneous condition would result to significantly greater decrease in PTSD severity than the sequential condition, when measured at 6- and 9-month follow up. With respect to aim 2, no specific hypothesis was formulated regarding differences in effectiveness on PTSD severity between the three active trauma-focused PTSD treatments (i.e. PE, EMDR and ImRs) at 6- and 9-month follow-up. No specific hypotheses were formulated for the secondary outcomes (Lortye

et al., 2021).

2. Methods

2.1. Study design

The TOPA (Treatment Of PTSD and Addiction) study is a single blind 6-arm randomized controlled trial (RCT) in patients with SUD and PTSD. Patients were allocated to simultaneous SUD + PE, SUD + EMDR or SUD + ImRs treatment or sequential SUD-PTSD-treatment (25% each). Next, sequential SUD + PTSD patients were randomly assigned to PE, EMDR, or ImRs (33% each). It therefore includes three simultaneous treatment groups (PE, EMDR, and ImRs) and three sequential treatment groups (starting with SUD treatment, followed by PE, EMDR, or ImRs). The study protocol received approval from the Medical Ethical Committee of the Amsterdam Academic Medical Centre (AMC) and was registered in the Netherlands Trial Register (NTR L7885). Comprehensive trial procedures and details have been published elsewhere (Lortye et al., 2021).

2.2. Participants

Participants were 209 patients who applied for SUD treatment and that were also diagnosed with co-occurring PTSD. Recruitment took place at two departments of Jellinek (Amsterdam and Utrecht), a major addiction treatment center in the Netherlands offering both inpatient and outpatient care according the principles of CBT, ACT or the 12Step Model. In total, 209 participants were included. The criteria for inclusion in the study were a) age 18 years or older; b) substance use disorder (s) according to the DSM-5 (American Psychiatric Association, 2013), with a primary diagnosis involving one of the following substances: alcohol, cannabis, cocaine (snorting), amphetamine, benzodiazepine, opioid; c) PTSD according to the DSM-5 criteria; d) sufficient understanding of the Dutch language to be able to fill out Dutch questionnaires and follow therapy in Dutch (Lortye et al., 2021). Exclusion criteria were a) acute psychotic disorder; b) intellectual disability (estimated IQ < 70); c) current physical or sexual abuse or death threats; d) high acute suicidal behavior (operationalized as current high suicidality score on the Mini-International Neuropsychiatric Interview as well as a serious suicide attempt within the past 3 months); e) life threatening self-mutilation; f) homelessness; g) involvement in a compensation case or legal procedures concerning admission or stay in the Netherlands; h) involvement in legal procedures regarding the index trauma; i) engagement in any other current PTSD treatment. The sample characteristics are presented in Table 1.

2.3. Procedure

Individuals seeking treatment at the addiction care departments were initially screened for PTSD using the Jellinek-PTSD questionnaire (van Dam et al., 2013) during intake. Those with positive screening results underwent a comprehensive PTSD evaluation with the CAPS-5 interview. Patients with a PTSD diagnosis received study information and may consent to be contacted for participation. Interested patients were invited for an inclusion interview, where inclusion and exclusion were screened and SUD was assessed using the SCID-5-S. All participants provided written informed consent. Eligible participants completed baseline assessments (T0) two weeks before initiating SUD treatment, which involved interviews and self-report questionnaires. Follow-up evaluations were conducted at 3 months (T1), 6 months (T2), and 9 months (T3) by junior researchers who were blinded to treatment conditions. Junior researchers received a comprehensive two-day training prior to data collection specifically for administering the CAPS-5 interview in which they observed and scored CAPS-5 assessments collaboratively and were continuously supervised throughout the study. No formal training was provided for the other self-report questionnaires, as

Table 1
Baseline characteristics of the study sample.

Characteristic	Total sample (N = 209)	Total sim (n = 158)	Total seq (n = 51)	Total PE (n = 70)	Total EMDR (n = 67)	Total ImRs (n = 72)
Age, years, mean (SD)	37.5 (11.99)	37.20 (12.10)	38.24 (11.75)	38.21 (13.56)	36.61 (10.73)	37.50 (11.60)
Female sex, %	46.4	46.8	45.1	42.9	56.7	40.3
Education level ^a , %						
1	25.3	24.1	29.5	20	26.9	29.2
2	41.6	43	37.3	48.6	34.3	41.7
3	31.6	32.3	29.4	30	37.3	27.8
Other	1.4	0.6	3.9	1.4	1.5	1.4
CAPS sum score, mean (SD)	37.35 (9.28)	37.38 (9.50)	37.28 (8.66)	36.50 (9.05)	38.21 (10.95)	37.39 (7.75)

Note. CAPS = clinician administered PTSD scale; EMDR = eye movement desensitization and reprocessing; ImRs = Imagery Rescripting; PE = Prolonged Exposure; PTSD = posttraumatic stress disorder; SD = standard deviation; seq = sequential; sim = simultaneous.

^a (1) no degree, primary school, secondary school lower level; (2) secondary school, higher level; (3) postsecondary.

these were completed independently by participants. After baseline assessment, participants were assigned to either simultaneous SUD-PTSD treatment (75% chance) or to sequential SUD-PTSD (25% chance). Subsequently, sequential SUD-PTSD treatment patients were randomly allocated to PE, EMDR of ImRs (33% chance each) as depicted in the trial flow (Fig. 1). These patients started PTSD treatment after three months. Post-randomization, participants were informed only of treatment timing (simultaneous versus sequential). The treatment type (PE, EMDR, ImRs) was only disclosed by the therapist at the first PTSD treatment session. Randomization was conducted by an independent researcher using a block randomization schedule after baseline, stratified by SUD treatment type and location.

2.4. Intervention

The simultaneous group (75%) started PTSD treatment within two weeks after baseline assessment and finished before 3-month follow-up. The sequential group (25%) started PTSD treatment within two weeks after 3-month follow-up and was completed before 6-month follow-up. All participants received treatment as usual for their SUD, which could vary in intensity and duration. Outpatient treatment involved one weekly session. Day treatment included three group sessions per week (5 h each) plus one individual session of 1 h. Inpatient treatment consisted of daily group sessions (4.5 h, 5 days a week) plus one weekly individual session for 6 weeks followed by 6 weeks of day treatment as described to the day program above. Treatment approaches consisted of either Cognitive Behavioral Therapy (CBT), Acceptance and Commitment Therapy (ACT), or the Minnesota 12-step model, with the option of adding medication-assisted support or detoxification as necessary. The treatment approach was determined through shared decision-making with the client following the intake assessment. All participants across the four treatment arms received consistent care in terms of timing and content. While abstinence was encouraged during PTSD treatment, it was not a requirement.

PTSD treatment consisted of 90-min sessions, conducted twice a week by two alternating therapists following a therapist rotation model (Van Minnen et al., 2018). All PTSD treatments included up to 12 sessions. To account for rescheduling due to cancellations or therapist absence, outcome assessments were planned up to three months after treatment start. This timing also minimized overlap with the PTSD treatment period, providing a clearer measure of treatment effect than a 6-week assessment, which for the CAPS would overlap with the final 4

weeks of treatment. A total of 35 therapists participated in the study, all trained in the three therapy types specifically for this trial by experts in each therapy (A. Van Minnen for Prolonged Exposure, E. ten Broeke for EMDR, and A. Arntz for ImRs). Before the trial began, at least two sessions from each therapy type were recorded and reviewed to ensure adherence to the protocols. Therapists attended weekly one-hour peer supervision sessions in groups of 6–8 and received annual 2-h expert supervision on each PTSD treatment. Additional trainer support was available upon request. All sessions were recorded, and 16 per treatment condition were randomly selected for fidelity assessment by blinded, trained junior researchers. Ratings (yes/no/not applicable) showed excellent interrater reliability (ICCs > 0.99). Treatments were clearly distinguishable (Cohen's $d > 5$) (Lortye et al., 2025). Although all these therapists also work as addiction counselors within the institution, the addition treatment for the included clients was always carried out by a different therapist. The PTSD therapists acted as co-therapists in this process.

All PTSD protocols consisted of 12 sessions. The first session in all PTSD treatments included psychoeducation and identifying key traumatic events. In the following sessions, 60 min were consistently dedicated to delivering the core intervention component specific to each treatment: imaginal exposure and in vivo exposure for PE, the standard EMDR procedure for EMDR, and the imagery rescripting protocol for ImRs. The remaining 30 min of each session were used for additional elements, including both protocol-based components, such as reviewing the treatment rationale, discussing homework and session evaluation, and non-protocol elements, such as completing questionnaires.

Prolonged Exposure (PE) therapy followed the Dutch translation (van Minnen & Arntz, 2017) of the protocol by Foa et al. (Foa et al., 2007), involving imaginal exposure (recounting trauma memories) and in vivo exposure (confronting real-life situations) to reduce trauma-related anxiety and used imaginal exposure every session and exposure in vivo as add-on every other session. Homework included listening to recorded sessions every day. EMDR therapy followed the Dutch adaptation of Shapiro's standard 8-phase protocol, focusing on reducing the intensity of traumatic memories by guiding the patient through eye movements while focusing on distressing images (Shapiro, 2018). ImRs therapy followed the protocol by Arntz and Weertman (Arntz & Weertman, 1999), which involves rescripting trauma memories to alter their emotional impact. During ImRs, the patient imagines the trauma as occurring in the present, then alters the sequence until the scene feels resolved. Both EMDR and ImRs can address trauma events that do not meet DSM-5 A-criteria. Therapists were actively involved in the rescripting process for 2–5 sessions while the patient viewed their younger self. Then, the patient reentered the image as their current self, reshaping the scene to meet the needs of their younger self. Other therapies or medication changes unrelated to SUD were discouraged, and participants were explicitly instructed not to begin any additional PTSD treatment until after the final follow-up.

2.5. Measurements

2.5.1. Primary outcome measures

PTSD severity was the primary study outcome, and was assessed at each evaluation using the Dutch version of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).

2.5.2. Secondary outcome measures

PTSD treatment completion (yes/no), was defined as attending all 12 sessions within three months or achieving early remission. SUD treatment completion (yes/no), was defined as someone who had completed the full SUD treatment or had stopped the treatment in mutual agreement with the addiction treatment team. Substance use problems in the last 3 months were measured with the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001) and Drug Use Disorders Identification Test (DUDIT) (Hildebrand, 2015). Additionally, we tested the

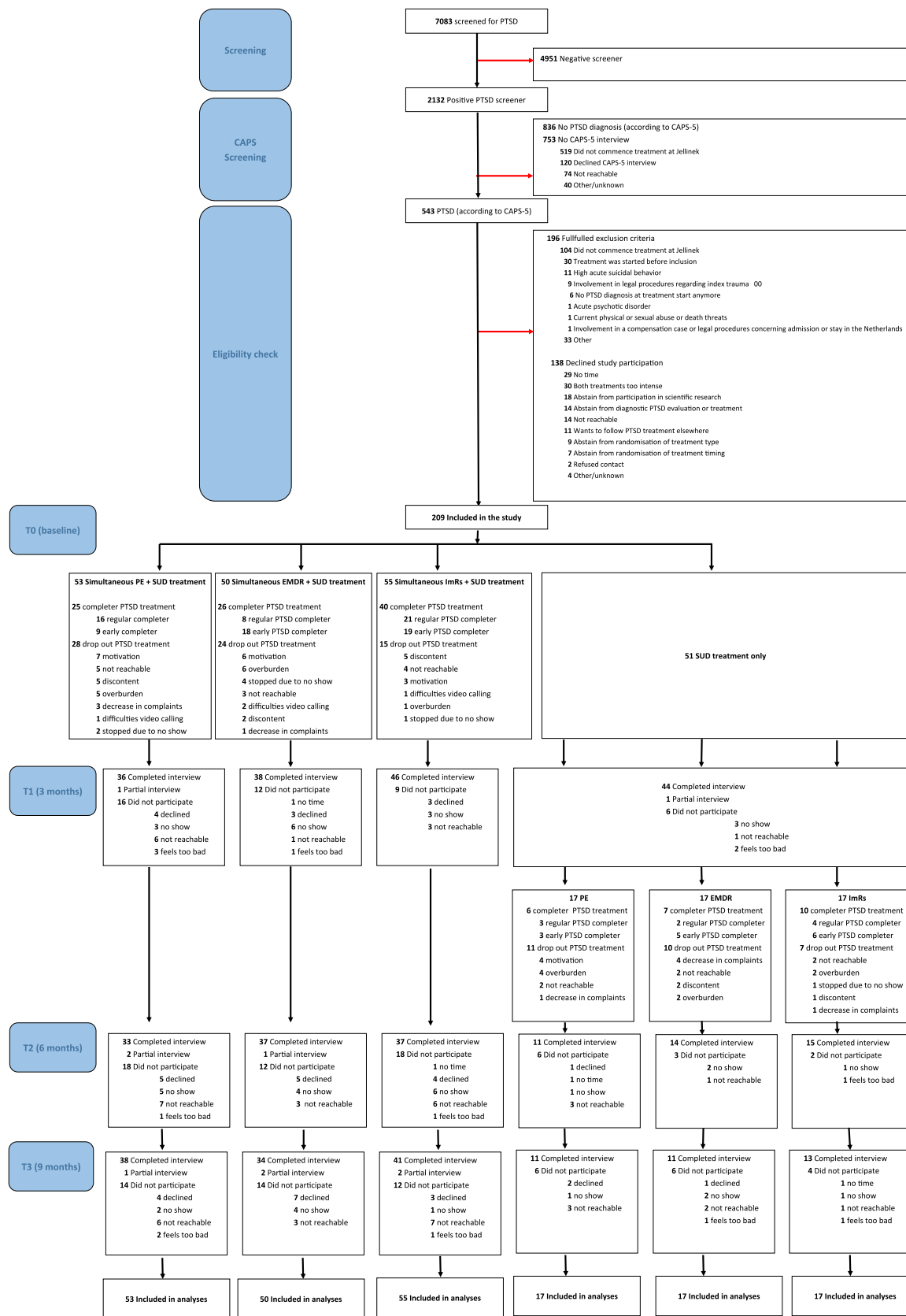


Fig. 1. Study flow chart.

overall model for the outcomes of loss of diagnosis (no longer meeting PTSD criteria of ≥ 1 B criterion, ≥ 1 C criterion, ≥ 2 D criterion and ≥ 2 E criterion) and full remission (CAPS-5 score < 12) (Larsen et al., 2020; Weathers et al., 2001). Non completion for PTSD treatment occurred if PTSD treatment was not completed within the allocated timeframe. Early completion was possible if 1) both therapist and patient concluded that the patient no longer experienced PTSD symptoms; 2) this was discussed with colleagues in weekly peer-supervision with at least one researcher included; 3) a total score below 13 on the PTSD checklist for DSM-5 (PCL-5) was present for two consecutive sessions, excluding four specific items (item 15, 16, 19, and 20) (Lortye et al., 2021). Information on SUD treatment completion was obtained from patient files. Finally, at baseline, patients' preference for timing and type of PTSD treatment were assessed. A Bayesian approach to the model outcome as well as other secondary outcomes will be published in a separate paper.

2.5.3. Other outcome measures

Demographic characteristics were collected during the inclusion interview: age, sex, country of birth, country of birth from the parents, relationship status, living situation and level of education. Furthermore, main SUD diagnoses were collected from patient files.

2.6. Statistical analysis

Analyses were performed according to the intention-to-treat principle. Analyses were conducted in R version 4.2.1. $P < .05$ was chosen as threshold for statistical significance. All reported P -values are two-tailed. Sample size calculation was published in the study protocol (Lortye et al., 2022).

Aim 1: To compare simultaneous treatment and sequential treatment of PTSD and SUD in terms of the continuous outcomes (CAPS-5, AUDIT, DUDIT), Linear Mixed Models (LMMs) with a two-level structure (repeated measures, patients) and a random intercept were used, implemented with R package lme4 version 1.1–32. First, the overall effect across the follow-up was evaluated with group allocation as a fixed effect and the baseline value of the particular outcome as covariate. Subsequently, between-group differences at the separate follow-up timepoints were evaluated by adding time (as a categorical variable represented by dummy variables) and an interaction between group and time to the model. For the primary outcome CAPS-5, the 6-month and 9-month follow-up timepoints were included, as the sequential group received PTSD treatment between the 3-month and 6-month follow-up. The analyses of the secondary outcome measures loss of PTSD diagnosis (yes/no) and full remission of PTSD (yes/no) were conducted with GLMMs for a binominal outcome with a logit link function. For the AUDIT and DUDIT, all follow-up timepoints (3-month, 6-month, and 9-month) were included, since all participants received SUD treatment before the 3-month follow-up. As post-hoc analysis, the LMMs with the CAPS-5 as outcome were repeated, including the 3-month timepoint, to examine whether potential treatment effects were obtained earlier in time. To compare simultaneous treatment and sequential treatment in terms of the dichotomous variables PTSD treatment completion and SUD treatment completion, two logistic regression analyses were conducted.

Aim 2: To compare PE, EMDR, and ImRs in terms of continuous outcome measures (CAPS-5, AUDIT, DUDIT), three LMMs were used for each outcome variable to make head-to-head comparisons (EMDR vs. PE; ImRs vs. PE; ImRs vs. EMDR), with a two-level structure (repeated measures, patients), with a random intercept. The overall effects across the follow-up period, as well as the between-group differences at separate timepoints, were evaluated in line with the procedure described above. To compare PE, EMDR, and ImRs in terms of the dichotomous outcomes PTSD treatment completion and SUD treatment completion, two logistic regression analyses were conducted for all three head-to-head comparisons.

Baseline data were complete. CAPS-5 T1 data was missing for 20.57% participants, T2 data was missing for 28.23% participants, T3

data was missing for 26.79% participants. No imputation of missing data was needed, since LMMs were applied for the continuous outcomes (Twisk & De Vente, 2008) and the dichotomous outcomes PTSD treatment completion and SUD treatment completion had no missing values.

3. Results

Recruitment occurred between September 19th, 2019, and May 4th, 2022, with a total of 209 participants being randomized. Baseline participant characteristics are presented in Table 1. The average baseline CAPS-5 score was 37.35 (SD = 9.28). The most common index traumas, in descending order, were child sexual abuse (26.3%), nonsexual child abuse (24.4%), adult nonsexual assault (20.1%), adult sexual assault (10%) and adult witnessing death and injury (8.1%).

3.1. Primary outcome

Table 2 shows no significant difference between simultaneous and sequential treatment in effectiveness on PTSD severity, when the 6-month and 9-month follow-up were included. No significant differences were found between the three types of PTSD treatment in

Table 2

Results from LMMs (for continuous outcomes) and logistic regression analyses (for treatment completion) to compare simultaneous treatment and sequential treatment.

Outcome		Simultaneous	Sequential	B (SE)	P
		(n = 158)	(n = 51)		
		Mean (SD)	Mean (SD)		
CAPS-5	Overall	NA	NA	1.22 (2.12)	0.566
	Baseline	37.38 (9.50)	37.27 (8.66)	NA	NA
	6-mo fu	12.28 (12.64)	15.38 (15.64)	1.56 (2.25)	0.489
	9-mo fu	12.82 (13.29)	14.91 (13.80)	0.80 (2.29)	0.727
CAPS-5 (post-hoc) ^a	Overall	NA	NA	4.97 (1.86)	0.008
	Baseline	37.38 (9.50)	37.27 (8.66)	NA	NA
	3-mo fu	15.79 (14.01)	27.16 (15.53)	11.38 (2.16)	<0.001
	6-mo fu	12.28 (12.64)	15.38 (15.64)	0.75 (2.24)	0.737
AUDIT	Overall	NA	NA	1.81 (0.96)	0.060
	Baseline	14.20 (11.93)	20.25 (12.84)	NA	NA
	3-mo fu	6.72 (7.56)	11.09 (11.26)	2.92 (1.20)	0.015
	6-mo fu	6.16 (5.98)	9.15 (9.35)	1.59 (1.23)	0.205
DUDIT	Overall	NA	NA	-0.15 (1.09)	0.885
	Baseline	19.35 (13.58)	14.04 (12.35)	NA	NA
	3-mo fu	7.33 (8.73)	7.42 (9.13)	1.01 (1.31)	0.442
	6-mo fu	6.82 (8.31)	5.23 (7.78)	-1.23 (1.36)	0.365
	9-mo fu	7.28 (8.45)	5.89 (9.17)	-0.54 (1.40)	0.698
	PTSD treatment completion	No. (%)	No. (%)	OR (95% CI)	P
	SUD treatment completion	86 (54.4)	32 (62.7)	1.41 (0.32–1.14)	0.299
				(0.74–2.70)	

Note. AUDIT = Alcohol Use Disorder Identification Test; CAPS = clinician administered PTSD scale; DUDIT = Drug Use Disorders Identification Test; MMs = Linear Mixed Models; NA = not applicable; SD = standard deviations; SE = standard error.

^a Post-hoc analysis: repeating the LMMs with the CAPS-5 as outcome, now including the 3-month timepoint.

effectiveness on PTSD severity (Table 3). Analysis of patients' treatment timing preferences at baseline revealed that 71.3% favored simultaneous treatment, compared to 9.6% who favored sequential treatment ($p < .001$).

3.2. Secondary outcomes

Table 2 shows no significant difference between simultaneous and sequential treatment on PTSD treatment completion. Participants in the ImRs condition were more likely to achieve PTSD treatment completion (69.4%) compared to both the PE condition (44.3%) and the EMDR condition (49.3%). EMDR did not statistically significantly differ from PE in terms of PTSD treatment completion.

As shown in Table 2, no significant difference was found between simultaneous and sequential treatment in effectiveness on alcohol and drug use problems, except for an effect on alcohol use problems, only at 3-month follow-up, favoring simultaneous treatment. For full remission, no significant difference between simultaneous treatment and sequential treatment was found, $\beta = -0.40$, $SE = 0.69$, $z = -0.58$, $p = .559$. For loss of diagnosis, no significant difference between simultaneous treatment and sequential treatment was found, $\beta = -0.11$, $SE = 1.47$, $z = -0.07$, $p = .943$. As shown in Table 3, no significant differences were found between the three types of PTSD treatment in effectiveness on alcohol and drug use problems. For full remission, no significant differences were found between EMDR and PE ($\beta = 0.10$, $SE = 0.70$, $z = 0.14$, $p = .891$), ImRs and PE ($\beta = -0.58$, $SE = 0.79$, $z = -0.73$, $p = .465$), and ImRs and EMDR ($\beta = -0.63$, $SE = 0.74$, $z = -0.85$, $p = .397$). For loss of diagnosis, no significant differences were found between EMDR and PE ($\beta = 0.49$, $SE = 1.58$, $z = 0.31$, $p = .756$), ImRs and PE ($\beta = 0.13$, $SE = 1.52$, $z = 0.09$, $p = .929$), and ImRs and EMDR ($\beta = -0.35$, $SE = 1.65$, $z = -0.22$, $p = .830$). No significant effects of treatment timing or PTSD treatment type on SUD treatment completion were found (see Tables 2 and 3).

3.3. Post hoc analysis

As shown in Table 2, when the 3-month follow-up timepoint was included in the comparison of simultaneous and sequential treatment, simultaneous treatment was more effective in reducing PTSD symptom severity compared to sequential treatment across the follow-up period. Significant between-group differences were found at 3-month follow-up in favor of simultaneous treatment, but no significant differences were found at 6-month and 9-month follow-up. This process was repeated for the outcomes of full remission and loss of diagnosis. Simultaneous

treatment was more effective in achieving full remission compared to sequential treatment across the follow-up period, $\beta = -0.97$, $SE = 0.44$, $z = -2.24$, $p = .025$. However, significant between-group differences were found at 3-month follow-up ($\beta = -2.65$, $SE = 0.75$, $z = -3.53$, $p < .001$), but no significant differences were found at 6-month ($\beta = -0.14$, $SE = 0.68$, $z = -0.21$, $p = .833$) and 9-month ($\beta = -0.41$, $SE = 0.70$, $z = -0.58$, $p = .564$) follow-up.

Simultaneous treatment was more effective in achieving loss of PTSD diagnosis compared to sequential treatment across the follow-up period, $\beta = -1.44$, $SE = 0.56$, $z = -2.58$, $p = .010$. However, significant between-group differences were found at 3-month follow-up ($\beta = -6.34$, $SE = 2.25$, $z = -2.82$, $p = .005$), but no significant differences were found at 6-month ($\beta = 0.09$, $SE = 1.33$, $z = 0.07$, $p = .947$) and 9-month ($\beta = -1.84$, $SE = 1.34$, $z = -1.37$, $p = .170$) follow-up.

4. Discussion

This study demonstrates that, in contrast to the hypothesis, simultaneous and sequential treatments do not significantly differ in decreasing PTSD symptoms when results were compared at follow up after 6- and 9-months (i.e. T2 and T3). However, when the 3-month follow-up was also included in the post hoc analyses together with the 6- and 9-months follow-up, simultaneous treatment was superior to sequential treatment in terms of PTSD severity (see Table 2). However, some of these between-group differences in PTSD outcomes at the 3-month follow up may partly reflect expectancy effects, whereby participants assigned to the sequential treatment condition did not anticipate improvement in their PTSD symptoms while awaiting the initiation of the designated PTSD intervention. Taken together, even though there is no significant difference when looked at longer term follow-up, simultaneous treatment has a faster effect compared to sequential treatment. Moreover, since most patients indicated they preferred simultaneous treatment, it can be argued to offer simultaneous treatment to patients who prefer this option. It is important to mention, however, that treatment timing was not related to being abstinent or not. In both conditions, abstinence was encouraged as much as possible, but it was not a requirement. Further investigation into this subject is important. For example, there is a need for comprehensive research to assess the effectiveness of immediately commencing PTSD treatment as opposed to delaying initiation until abstinence is achieved. Interestingly, the study demonstrates a plateau effect after three months of treatment, which is in contrast with long-term efficacy found in PTSD treatment (Kline et al., 2018). An explanation for these results could be that patients with comorbid SUD may benefit from early gains in more

Table 3

Results from LMMs (for continuous outcomes) and logistic regression analyses (for treatment completion) to compare three active PTSD treatments head-to-head.

Outcome		PE (n = 70)	EMDR (n = 67)	ImRs (n = 72)	EMDR vs. PE	P	ImRs vs. PE	P	ImRs vs. EMDR	P
		Mean (SD)	Mean (SD)	Mean (SD)	B (SE)		B (SE)		B (SE)	
CAPS-5	Overall	NA	NA	NA	-2.13 (2.36)	0.367	-0.79 (2.29)	0.731	1.46 (2.13)	0.491
	Baseline	36.50 (9.05)	38.21 (10.95)	37.39 (7.75)	NA	NA	NA	NA	NA	NA
	6-mo fu	13.98 (14.01)	12.92 (13.84)	12.52 (12.97)	-2.33 (2.49)	0.349	-1.70 (2.48)	0.492	0.73 (2.28)	0.747
	9-mo fu	14.04 (15.46)	11.81 (11.11)	13.89 (13.29)	-2.04 (2.49)	0.412	0.01 (2.43)	0.996	2.20 (2.29)	0.336
AUDIT	Overall	NA	NA	NA	0.24 (0.51)	0.641	-0.54 (1.06)	0.611	0.94 (0.89)	0.290
	Baseline	17.50 (12.74)	14.49 (11.85)	15.00 (12.55)	NA	NA	NA	NA	NA	NA
	6-mo fu	7.43 (6.24)	6.71 (7.79)	6.79 (7.32)	-0.15 (0.62)	0.811	-0.48 (1.33)	0.716	0.02 (1.17)	0.986
	9-mo fu	7.76 (8.00)	5.36 (3.99)	7.07 (7.70)	0.67 (0.63)	0.285	-0.58 (1.29)	0.652	1.93 (1.18)	0.104
DUDIT	Overall	NA	NA	NA	0.42 (0.57)	0.461	0.22 (1.34)	0.871	0.51 (1.31)	0.696
	Baseline	19.30 (13.36)	16.73 (13.08)	18.08 (13.95)	NA	NA	NA	NA	NA	NA
	6-mo fu	7.61 (8.39)	6.29 (7.11)	5.40 (8.94)	0.10 (0.65)	0.881	0.34 (1.52)	0.820	-0.22 (1.41)	0.877
	9-mo fu	7.73 (8.13)	5.62 (6.27)	7.33 (10.47)	0.77 (0.66)	0.246	0.12 (1.48)	0.938	1.26 (1.42)	0.375
		No. (%)	No. (%)	No. (%)	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
PTSD treatment completion	31 (44.3)	33 (49.3)	50 (69.4)	1.22 (0.62-2.39)	0.560	2.86 (1.44-5.69)	0.003	2.34 (1.17-4.68)	0.016	
SUD treatment completion	40 (57.1)	38 (56.7)	40 (55.6)	0.98 (0.50-1.93)	0.960	0.94 (0.48-1.82)	0.849	0.95 (0.49-1.87)	0.890	

Note. AUDIT = Alcohol Use Disorder Identification Test; CAPS = clinician administered PTSD scale; CI = confidence interval; DUDIT = Drug Use Disorders Identification Test; EMDR = Eye Movement Desensitization and Reprocessing; ImRs = Imagery Rescripting; NA = not applicable; OR = odds ratio; PE = Prolonged Exposure; PTSD = posttraumatic stress disorder; SD = standard deviation; SE = standard error; SUD = substance use disorder.

acute symptoms, while the complex and persistent symptoms associated with chronic substance use, such as changes in brain function, stress regulation, and emotion management, may limit further progress.

Furthermore, although a previous article about this study showed that EMDR and ImRs yielded more robust results than PE in this population (Lortye et al., 2025), no significant differences were found in a direct comparison of the effectiveness of all three types of treatment (PE vs EMDR vs ImRs) when looked at 6- and 9-month follow up (T2 and T3). In advance, patients preferences were EMDR (32.1%), followed by PE (25.4%) and ImRs (16.7%). Only preference between EMDR and ImRs differed significantly ($p = .002$) in favor of EMDR.

With regard to the secondary outcome of PTSD treatment completion, simultaneous and sequential treatment did not differ significantly. An explanation for this finding could be that regardless of the timing of the PTSD treatment, patients with SUD and PTSD in general have difficulty remaining in active treatment (Lewis, Roberts, Gibson, & Bisson, 2020; Simpson et al., 2021). However, since the sample size was set up to detect a medium effect size, the statistical power was insufficient to detect a small effect between the simultaneous (57.6%) and the sequential (45.1%) group. The results are in line with Kehle-Forber et al., who also did not found a significant difference between integrated and sequential treatment (Kehle-Forbes et al., 2019). However, their integrated treatment is not directly comparable to the simultaneous treatment in this study, given that their integrated SUD + PTSD treatment involved a single therapist and utilized different treatment modalities than those employed in this study.

Concerning the three treatment types (e.g. PE vs EMDR vs ImRs), ImRs was associated with significantly higher treatment completion rate than PE and EMDR. For PE (44.3%) and EMDR (49.3%), treatment completion numbers are somewhat comparable to previous studies (Simpson et al., 2021) and treatment completion for ImRs (69.4%) is notably higher. However, there is no uniform definition of treatment completion in the literature, with most previous studies defining treatment completion as a certain percentage of sessions that must be achieved (Kline et al., 2022). However, in this study, the aim was to make a content-based assessment for each client to determine whether they were an early responder, with treatment completion defined as attending all sessions within a 3-month timeframe or fulfilling the definition of early responder. Therefore, treatment completion more accurately reflects meaningful engagement with the intervention, whereas definitions based on minimal attendance thresholds (e.g., attending a minimal number of sessions) may not fully reflect “real world” treatment completion following attainment of clinical benefit. A threshold-based definition (e.g., ≥ 8 sessions) can be problematic for two reasons: (1) participants may meet the attendance threshold but discontinue treatment against clinical advice while having achieved limited therapeutic improvement, and (2) participants may achieve the intended clinical benefit before reaching the threshold. By using the current definition, we sought to represent treatment completion in routine clinical practice more precisely. These findings suggest that while there was no significant difference in treatment effect (i.e. PTSD severity) between the three different treatment types at 6- and 9-month follow up, ImRs may be more effective in maintaining patient retention. This could suggest that PE is particularly effective for those who completed it, thereby compensating for attrition effects at the group level. Moreover, the relation between treatment outcome and treatment completion is not necessarily a linear correlation as already hypothesized in a previous study (Hien et al., 2012). Finally, the study could have lacked sufficient power to detect modes between-group differences.

Finally, no differences were found in SUD outcomes between simultaneous and sequential treatment, except the improvement with regard to alcohol use problems favoring the simultaneous group over the sequential group, albeit solely evident at the 3-month follow up. This is in line with a previous report of this study on the short-term effects, in which none of the combined SUD and trauma-focused PTSD treatments

showed significant improvements in SUD outcomes compared to manualized SUD treatment alone at the 3-month follow-up (Lortye et al., 2025). Importantly, this also indicates that the addition of trauma-focused therapy did not adversely affect SUD treatment outcomes.

In conclusion, although no significant differences were found between the treatments, the results suggest that simultaneous treatment may be a faster option for patients and is preferred by most patients. Therefore it can be argued to offer simultaneous treatment to patients that prefer this over sequential treatment. Moreover, offering all three treatment types and making decisions in collaboration with patients, taking into account their preferences and previous treatment dropout, is recommended.

4.1. Strengths and limitations

This is the first study to compare both timing and type of PTSD treatment in patients with co-occurring SUD and PTSD. Moreover, also outside of this sample, PE, EMDR, and ImRs have not been directly compared before. Additionally, the study has a substantial sample size, extended follow-up period, inclusive criteria, a socio-economically diverse participant pool, and minimal attrition. Moreover, the implementation of well-established PTSD treatment protocols ensures the findings are relevant to routine clinical practice. The considerable heterogeneity in type and dose of SUD treatment reflects the diversity of real-world clinical practice, which is a strength, but also a limitation; to address this, stratification for treatment intensity and location was applied during randomization to reduce its impact on group comparisons.

There are also some limitations. It is important to note that smaller than medium effect sizes could not be identified due to the study's statistical power that was set up to find medium to large effects. The sample size also precluded investigating whether timing (simultaneous vs sequential) interacted with type of PTSD-treatment. Owing to the COVID-19 pandemic, in-person interventions were substituted with video calls, while maintaining the same treatment protocol. Potential influence of the pandemic on treatment outcomes cannot be excluded. Finally, although research assistants received extensive training prior to the trial and ongoing supervision throughout the study, a limitation is that formal fidelity calculations were not conducted for the CAPS-5. On the other hand, self-reported PTSD severity showed similar results, supporting the validity and reliability of the CAPS ratings.

4.2. Conclusions and clinical implications

In conclusion, simultaneous and sequential treatment did not show significant differences in PTSD severity and treatment completion. While there was no significant difference in PTSD severity changes between treatment type (PE vs EMDR vs ImRs), ImRs demonstrates significantly higher treatment completion than PE and EMDR. Overall, PTSD treatment did not enhance SUD outcomes. It can be concluded that besides PE, EMDR and ImRs are effective treatment options for patients with co-occurring SUD-PTSD. Both simultaneous as well as sequential treatment are effective treatment options. Shared decision-making is recommended for both the timing and type of treatment, taking into account patient preferences, previous dropout experiences, results on effectiveness and treatment retention, and the available treatment options.

CRedit authorship contribution statement

Sera Lortye: Writing – original draft. **Nathalie N.M. Faber:** Writing – review & editing. **Joanne P. Will:** Investigation. **Loes A. Marquenie:** Writing – review & editing. **Nick M. Lommerse:** Software. **Anna E. Goudriaan:** Writing – review & editing. **Arnoud Arntz:** Writing – review & editing. **Marleen M. de Waal:** Writing – review & editing.

Clinical trial registration details

This study protocol was approved by the Medical Ethical Committee of the Amsterdam Academic Medical Centre (AMC) and was registered at 'Netherlands Trial Register' (NTR L7885).

Primary funding

This work was funded by the Dutch 'Stichting tot steun VCVGZ' who assigned a grant to Prof.dr. Arnold Arntz, dr. Marleen de Waal, dr. Loes Marquenie and Prof.dr. Goudriaan at the University of Amsterdam [grant number 244]. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

All participants, trainers, therapists, and research assistants contributing to the study. Jellinek treatment centers Amsterdam and Utrecht.

Data availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [M.M. de Waal, m.m.dewaal@amsterdamumc.nl] upon reasonable request after the completion of this study.

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